IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: **Robert W. Finberg *et al.***

Serial No.: **09/486,970**

Filed: **March 2, 2000**

For: **THE USE OF AGENTS WHICH BIND G PROTEINS FOR TREATING SEPTIC SHOCK**

Attorney Docket No.: **DFN-025US**

Examiner: Russel, J.

Group Art Unit: 1653

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Commissioner for Patents
Washington, D.C. 20231

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December 11, 2001
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By: _____
DeAnn F. Smith, Esq.
Registration No. 36,683
Attorney for Applicant

AMENDMENT AND RESPONSE

Dear Sir:

This is in response to the Office Action dated June 26, 2001 (Paper No. 6). A separate request for the appropriate extension of time is being filed concurrently herewith. Responsive to the Office Action, please amend the application as follows:

In the Specification:

Please insert the following paragraph after the title at page 1 of the specification:

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--Related Applications

This application claims priority to PCT International Application PCT/US98/18432 filed on September 4, 1998 which claims priority to U.S. Provisional Application 60/057,941 filed on September 5, 1997, the contents of which are expressly incorporated herein by reference.--

A1

Please replace the paragraph beginning at page 1, line 12, with the following:

--Septic patients usually die as a result of poor tissue perfusion and injury followed by multiple organ failure. It is well recognized that many of the responses that occur during septic shock are initiated by bacterial endotoxin, a glycolipid antigen present on the surface of gram negative bacteria. This endotoxin (also referred to herein as lipopolysacchride or LPS) is released upon the death or multiplication of the bacteria and is known to activate monocytes/macrophages or endothelial cells causing them to produce various mediatior molecules such as toxic oxygen radicals, hydrogen peroxide, tumor neurosis factor-alpha (TNFα), and interleukin (IL-1, IL-6, and IL-8). These cellular and humoral inflammatory mediators evoke septic shock with symptoms ranging from chills and fever to circulatory failure, multiorgan failure, and death.--

A2

Please replace the paragraph beginning at page 1, line 22, with the following:

--The impact of sepsis is particularly devastating to patients with compromised cardiac and hepatic function and to immunocompromised patients. Patients at high risk are elderly, chemotherapy patients and those requiring surgery or invasive instrumentation. The current therapy of antibiotics and hemodynamic support has not proven to be successful. An improved method for treating or preventing septic shock would be of great value.--

A3

Please replace the paragraph beginning at page 2, line 30, with the following:

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--Accordingly, this invention provides compositions and methods for treating or preventing septic shock in a subject at risk of developing septic shock The method comprises administering an effective amount of an agent which binds G protein such that septic shock is treated or prevented in the subject. The agents which bind G protein are useful for both prophylactic and/or therapeutic treatments of septic shock.--

A4

Please replace the paragraph beginning at page 3, line 24, with the following:

--Figure 4 shows that mastoparan only inhibits CD14-dependent LPS-induced signal transduction in U373-CD14 transfected cells.--

A5

Please replace the paragraph beginning at page 5, line 24, with the following:

--The term "administering" is intended to include routes of administration which allow the agent to perform its intended function of treating or preventing septic shock by binding to G protein. Examples of routes of administration which can be used include parenteral injection (*e.g.*, subcutaneous, intravenous, and intramuscular), intraperitoneal injection, oral, inhalation, and transdermal. The injection can be bolus injections or can be continuous infusion. Depending on the route of administration, the agent can be coated with or disposed in a selected material to protect it from natural conditions which may detrimentally affect its ability to perform its intended function. When the agent is a peptide, such as mastoparan or analog thereof, the peptide can be modified at one or more of its termini to protect the peptide from degradation. Methods of protecting peptides from degradation are disclosed in U.S Patent No. 5,589,568 which is incorporated herein by reference. The agent can be administered with other agents and/or with a pharmaceutically acceptable carrier. Further, the agent can be administered as a mixture of agents which bind G proteins, which also can be coadministered with a pharmaceutically acceptable carrier. The agent can be administered prior to the onset of septic shock or after the onset of septic shock.--

A6

Please replace the paragraph beginning at page 6, line 17, with the following:

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--The regimen of administration can affect what constitutes an effective amount. G protein binding agents can be administered to the subject either prior to or after the onset of septic shock. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused or can be a bolus injection. Further, the dosages of the G protein binding agent(s) can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.--

A7

Please replace the paragraph beginning at page 9, line 15, with the following:

--**Isolation of human PBMC and monocytes.**

Freshly isolated human peripheral blood mononuclear cells (PBMC) and monocytes were obtained from leukopaks (discarded leukocyte from platelet donations). The cells were fractionated on FICOLL-HYPAQUE™ gradients, washed, treated with tris-buffered NH_4Cl to eliminate RBCs and washed to obtain PMBCs. Monocytes were obtained by depleting the PBMCs of T cells and NK cells by negative selection asking standard techniques. T cells and NK cells were removed by treatment with anti-CD3 and anti-CD2 monoclonal antibodies followed by goat anti-mouse Ig conjugated magnetic beads at a 10:1 bead:cell ratio. The monocyte preparations were at least 80-85% monocytes, as determined by anti-CD14 staining and forward and slide light scatter analysis using a FACScan (Becton-Dickenson, Elmhurst, IL). Less than 2% of the contaminating cells in the monocyte preparation were T cells and no NK cells could be detected. Monocytes were maintained in Ham's F-12 10% FCS, L-Glutamine and penicillin/streptomyocin at 37°C in 5% CO_2.--

A8

Please replace the paragraph beginning at page 11, line 16, with the following:

--**Lethal endotoxin shock**

A9

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